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Author(s)	Klick, BA; Durrani, S; Chan, KH; Ip, DKM; Chou, SK; Kwok, HKH; Ng, S; Chiu, SSS; Peiris, JSM; Leung, GM; Cowling, BJ
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**Live attenuated seasonal and pandemic influenza vaccine in school-age children:
A randomized controlled trial**

Brendan Klick¹, Sunita Durrani¹, Kwok-Hung Chan², Dennis K. M. Ip¹, Erica
S. K. Chou¹, Henry K. H. Kwok³, Sophia Ng¹, Susan S. Chiu⁴, J. S. Malik Peiris^{1,6},
Gabriel M. Leung¹, Benjamin J. Cowling¹

Affiliations:

1. School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.
2. Department of Microbiology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.
3. Occupational Medicine Service, Queen Mary Hospital, Hong Kong Special Administrative Region, China.
4. Department of Pediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong Special Administrative Region, China.
6. Centre for Influenza Research, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China.

Corresponding author:

Benjamin J. Cowling, School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 21 Sassoon Road, Pokfulam, Hong Kong.

Tel: +852 3906 2011; Fax: +852 3520 1945; email: bcowling@hku.hk

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ABSTRACT

Background: The novel influenza A(H1N1pdm09) virus emerged in North America in early 2009 and rapidly spread worldwide. In this study we report the efficacy of the live attenuated monovalent H1N1pdm09 vaccine and 2009-10 seasonal influenza vaccine in a randomized double-blind placebo-controlled trial.

Methods: We enrolled 703 children aged 7-11. Each child was randomly allocated in the ratio 3:2 to receive one dose of live attenuated monovalent H1N1pdm09 vaccine or saline placebo between November 2009 and January 2010, followed after 3-10 weeks by independent random allocation to one dose of live attenuated trivalent 2009-10 seasonal influenza vaccine or saline placebo in the same ratio. Children were followed up through September 2010 with biweekly telephone calls and symptom diaries. Seasonal and pandemic influenza infections were confirmed by virologic testing of nose and throat swabs collected during acute respiratory illnesses.

Results: Overall, 30 children had confirmed influenza including 3 (0.43%) H1N1pdm09, 10 (1.4%) seasonal A(H3N2), and 17 (2.4%) influenza B. There were no significant differences in incidence rates of H1N1pdm09 or A(H3N2) between the four study arms, but receipt of the seasonal influenza vaccine was associated with a significant reduction in risk of influenza B ($p < 0.01$). Vaccine efficacy against confirmed H1N1pdm09 infection associated with receipt of the monovalent H1N1pdm09 vaccine was 65% (95% confidence interval, CI: -281%, 97%). Vaccine efficacies against confirmed seasonal influenza A(H3N2) and B infection associated with receipt of the seasonal influenza vaccine were 31% (95% CI: -138%, 80%) and 96% (95% CI: 67%, 99%) respectively.

Conclusions: Vaccine efficacy was consistent with other studies of the monovalent H1N1pdm09 vaccine and seasonal influenza vaccines. Our study was underpowered

to provide precise estimates of vaccine efficacy due to low incidence of influenza A viruses during the study period.

INTRODUCTION

Influenza vaccination is effective in reducing influenza-related morbidity in school-age children in years when the vaccine strains are well-matched to circulating viruses [1,2]. In early 2009 a novel pandemic influenza A(H1N1pdm09) virus emerged in North America and rapidly spread to other countries. A monovalent vaccine against the novel strain became available after 4-6 months. Preliminary studies confirmed the safety, tolerability, and immunogenicity of a monovalent intranasal live attenuated H1N1pdm09 vaccine [3]. There is some evidence that the monovalent H1N1pdm09 vaccine has moderate to high vaccine effectiveness against confirmed infection [4-13].

We conducted a double-blind placebo-controlled randomized trial to evaluate the efficacy of the live attenuated H1N1pdm09 vaccine and 2009-10 seasonal trivalent influenza vaccine.

METHODS

This large school-based double-blind placebo-controlled randomized controlled trial was conducted in Hong Kong over a 1-year period from September 2009 through September 2010. The primary objective of the study was to evaluate the efficacy of vaccinating school-age children against seasonal influenza, H1N1pdm09, or both, in reducing confirmed influenza infections among school-age children. The study was also designed to investigate indirect benefits of influenza vaccination of study subjects to their household contacts and classmates, which will be reported separately.

Enrolment, randomization, and follow-up

We attempted to contact the principals of all 615 primary schools in Hong Kong by mail and telephone during the summer of 2009, provided information about our study and invited them to participate in our study. In interested schools we organized health talks which including an invitation to participate in our study either as stand-alone events or as part of school open days during September and October 2010.

Information regarding the child's health status was collected from interested parents. All children aged 7 to 11 were eligible to participate unless they had asthma or active wheezing, a history of hypersensitivity to eggs or other substances in the vaccine or if any household member were receiving immunosuppressive agents or had an underlying immune-compromised condition. We obtained signed informed consent forms from the parents of children who met the inclusion criteria and were willing for their child to participate.

Children were randomly allocated to receive either one dose of pandemic influenza vaccine or placebo during November and December 2009 at specially arranged in-school clinics. Individual classes were allocated to blocks of vaccine:placebo in ratios of either 4:1 or 2:3 with equal chance, and within classes children were randomized within blocks of size 5 so that the overall ratio of vaccine:placebo was 3:2. Allocation lists were thus constructed for each of the two strata and used in sequence. The motivation for including two strata with differing randomization ratios was to allow inferences to be made about indirect benefits of vaccination via comparison of the incidence of infections in the control arms across the two strata. After one month all study subjects who received H1N1pdm09 vaccine were matched to receive seasonal trivalent vaccine, and subjects who received placebo were matched to receive a

second dose of placebo. However as a result of improper implementation of the randomization scheme, the receipt of seasonal influenza vaccine or placebo occurred independently of the original allocation of pandemic vaccine, resulting in four randomized study arms: pandemic plus seasonal vaccine, pandemic vaccine plus placebo, placebo plus seasonal vaccine, or two placebo doses in the ratio 2:1:1:1 (16:4:4:1 and 4:6:6:9 in the two strata where vaccine:placebo equals 4:1 and 2:3, respectively).

Immediately prior to vaccine administration, a physician confirmed the fitness of each study subject to receive vaccine. Subjects were provided with a 7-day adverse reaction card following receipt of each vaccine. We arranged to revisit schools at later dates to administer vaccines to study subjects who were deemed unfit at the first visit. Blinding of study vaccines was achieved by using identical packaging of vaccines and placebo in numbered syringes. A research assistant who had no knowledge of treatment assignments allotted unique identification codes to each participant. Vaccine allocations were not revealed to the subjects, their parents and household members, the study team responsible for vaccine administration and subject follow-up, or the laboratory staff.

Subjects were provided with symptom diary cards to record signs and symptoms associated with acute respiratory illness (ARI) from recruitment to the study until 30 September 2010. The diary cards were posted back on a monthly basis in prepaid envelopes. We conducted biweekly telephone follow-up throughout the follow-up period to prospectively identify ARI episodes. Participating households were also encouraged to proactively call our study hotline directly if any member was suffering

from an ARI. A report of ARI in any household member triggered a home visit from one of our study nurses during which nose and throat swabs were collected from all household members regardless of illness. Home visits were repeated at 3-day intervals until illnesses resolved. Households were compensated with supermarket coupons or book tokens worth US\$65 for participation in the study. Participants were compensated with US\$6.5 for each nose and throat swab sample provided. The study was approved by the Institutional Review Board of Hong Kong University.

Vaccines and placebos

We obtained special permission from the Hong Kong Department of Health to import the vaccines into Hong Kong for this study. Live attenuated H1N1pdm09 vaccine (Influenza A (H1N1) 2009 Monovalent Vaccine Live, Intranasal, MedImmune LLC) and trivalent live attenuated 2009-10 seasonal influenza vaccine (FluMist, MedImmune LLC) were not licensed in Hong Kong at the start of our study; the 2010-11 live attenuated seasonal influenza vaccine was subsequently licensed for use in Hong Kong. The only influenza vaccines licensed and locally available at the start of our study were trivalent inactivated influenza vaccines. A monovalent inactivated H1N1pdm09 vaccine became available in January 2010 but community uptake was very low.

Each 0.2ml pre-filled refrigerated H1N1pdm09 vaccine sprayer contained $10^{6.5-7.5}$ fluorescent focus units of the live attenuated influenza virus reassortant of the pandemic virus A/California/7/2009 (H1N1). Each 0.2ml trivalent seasonal influenza vaccine sprayer contained $10^{6.5-7.5}$ fluorescent focus units of live attenuated influenza virus reassortants of these three strains for the 2009-10 season: A/South

Dakota/6/2007 (H1N1) (A/Brisbane/59/2007-like), A/Uruguay/716/2007 (H3N2) (A/Brisbane/10/2007-like), and B/Brisbane/60/2008. Placebos were composed of 0.2ml saline in identical pre-filled sprayers.

Laboratory methods

Our protocols for collection of nose and throat swabs during home visits have been described in detail elsewhere [14-17]. Following collection, swabs were suspended in a tube containing viral transport medium (0.5% bovine serum albumin in Earle's balanced salt solution with antibiotic), stored in an ice box with at least two icepacks, and transferred within 3 hours to the central testing laboratory at Queen Mary Hospital by courier at 4-8°C. Specimens were eluted and cryopreserved at -70°C immediately after receipt in the laboratory prior to testing. Specimens were tested by reverse transcription polymerase chain reaction (RT-PCR) for influenza A and B viruses and subtyped using standard methods as described previously [14-19].

Outcome measures

The primary outcome measures were influenza A or B virus infection confirmed by RT-PCR, and the number of episodes of ARI, defined as any 2 of the following 5 signs or symptoms: fever $\geq 37.8^{\circ}\text{C}$, cough, headache, sore throat, or myalgia. A secondary outcome measure was the number of episodes of febrile acute respiratory illness (FARI), defined as fever $\geq 37.8^{\circ}\text{C}$ plus cough or sore throat [14,15]. Thus FARI episodes were a subset of ARI episodes. We counted all episodes that were reported via symptom diaries or the telephone follow-up from two weeks after receipt of the first vaccine (H1N1pdm09) or placebo dose until 30 September 2010, excluding the two week period following receipt of the second vaccine (seasonal) or placebo dose.

We defined new ARI episodes as episodes that began at least 7 days after the end of a previous ARI episode. Vaccine reactogenicity was assessed in terms of 12 signs or symptoms measured on a scale of none/mild/moderate/serious for 7 days following vaccination.

Statistical analysis

This study was originally planned as a larger 2-year study with two arms, vaccine versus placebo, but these plans were revised in light of the emergence of the pandemic. For the purposes of power analysis, if we conservatively assumed no synergy or cross-strain protection between vaccines, randomization of 420 children to H1N1pdm09 vaccine versus 280 to placebo would allow 80% power to identify vaccine efficacy of 50% assuming a cumulative incidence of confirmed H1N1pdm09 infection of 15% in the placebo arm, or vaccine efficacy of 66% assuming a cumulative incidence of 7.5% in the placebo arm. Power would be reduced for lower efficacy or lower attack rates. A similar power calculation applies for specific strains contained in the seasonal vaccine. Cross-strain protection or synergy between vaccines would increase the power of the study to detect the efficacy of one or both vaccines.

The proportion of children with a confirmed influenza infection were compared using Fisher's exact tests. Because children could have more than one episode and could differ in duration of follow up, the rate of ARI or FARI episodes were modeled using Poisson regression and rates between study arms were compared using Wald tests from nested models. Confidence intervals for incidence rates were estimated using exact Poisson confidence intervals [20]. We estimated vaccine efficacy as (1-

cumulative incidence ratio) $\times 100$. For analyses of vaccine efficacy against confirmed influenza B where there was a zero in the numerator, we added 0.5 to each cell before calculating the relative rate as an ad-hoc correction [21,22]. Analyses were conducted in accordance with the intention to treat principle. For all hypothesis tests, a p-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted in R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

MedImmune LLC supported the study by providing an unrestricted research grant, live attenuated vaccines, and saline nasal sprayers. The funding body had no role in study design, data management, analysis or interpretation of the data, or the decision to submit for publication.

RESULTS

The principals of 615 primary schools across Hong Kong were invited to participate, 50 school principals expressed preliminary interest in our study and 34 schools subsequently agreed to participate. Invitation letters were sent to all the parents of children aged 7-11 years old in 34 schools. Seven schools discontinued participation following a low response rate from parents; the study proceeded in 27 primary schools that had a total student population of around 16,300 children. The parents of approximately 3,000 children expressed an interest to attend the health talk; approximately 1,500 parents attended one of our health talks. The parents of 923 children provided signed informed consent to participate in our study. Subsequently 168 children were withdrawn prior to randomization most commonly due to concerns

over vaccine safety following media speculation on adverse events associated with H1N1pdm09 vaccines, 25 subjects were found to be ineligible most commonly due to asthma, and 27 subjects were unfit to receive vaccination for various reasons, the most common being current acute respiratory illness.

In total, 703 children were randomized and received a single dose of H1N1pdm09 vaccine or placebo, and 685 children subsequently received seasonal vaccine or placebo. One child was found to be ineligible due to an acute ARI during the scheduled appointment for seasonal vaccination, and the parents of 17/703 children withdrew from the study after H1N1pdm09 vaccination but prior to administration of seasonal vaccination. Five children were lost to follow-up after receipt of seasonal vaccine. The number of participating children in any class was no greater than 9 and most frequently 1-5 within classes of 26-35 children. In accordance with the intention-to-treat principle all 703 randomized children in the four study arms were included in subsequent analyses. Figure 1 summarizes the flow of subjects through the study.

Baseline characteristics of study subjects were similar across the four arms and the majority of children were aged 9-11y (Table 1). Of the children aged ≤ 8 y, 69/229 (30%) had received influenza vaccination for the preceding 2008-09 season. We administered vaccines during the period of low influenza activity prior to a winter influenza season dominated by influenza B with some H1N1pdm09 circulation, and a summer influenza season later than usual and dominated by drifted A/Perth/16/09-like influenza A(H3N2) viruses that were antigenically different to the vaccine A(H3N2) strain (Appendix Figure 1). 448/685 (65%) children received the second vaccination

21-59 days after the first vaccination, 190/685 (28%) children received the second dose after 60-74 days, 46/685 (7%) children received the second vaccination after 75-92 days, and one child received the second vaccination after a 14-day delay.

No serious adverse events were reported following vaccination, and adverse events were uncommon. 85% of all reported adverse events were graded as mild rather than moderate. The most frequently reported adverse event following receipt of H1N1pdm09 vaccine and seasonal vaccine was nasal congestion (Appendix Figure 2). Rates of adverse events were generally higher for the H1N1pdm09 vaccine than the seasonal vaccine. There was a statistically significant difference in occurrence of nasal congestion, sore throat, abdominal pain and chills between seasonal vaccine and placebo, but there were no other statistically significant differences in frequency of reported adverse events between vaccines and placebos.

We collected 1,630 nose and throat swabs from 317 study subjects during the follow-up period, including 1,051 (64%) swabs that were collected during an ARI episode in the subject, and 579 collected while a household contact had ARI. 30 children had influenza virus infection confirmed by RT-PCR: 3 (0.43%) had H1N1pdm09, 10 (1.4%) had seasonal A(H3N2), and 17 (2.4%) had influenza B. Of the confirmed H1N1pdm09 infections, 2/3 occurred 47 and 35 days after receipt of H1N1pdm09 vaccine or the matched placebo, respectively, but prior to receipt of seasonal vaccine. No confirmed seasonal influenza infections occurred during the window between receipt of the two vaccines. There were no statistically significant differences between study arms in H1N1pdm09 or H3N2 incidence, but there was a statistically significant reduction in influenza B incidence in the study subjects who received the seasonal

influenza vaccine (Table 2). Of the confirmed infections, 30 (100%) were associated with a reported ARI episode including 27 (90%) associated with a FARI episode. Study subjects reported 945 ARI episodes including 383 FARI episodes during the follow-up period, with statistically significant differences in all-cause risk of acute respiratory illnesses between study arms (Table 2). Results were similar when analyses were stratified by age into children aged 7-8 or 9-11 years (data not shown).

Vaccine efficacy estimates are shown in Table 3. Efficacy against confirmed H1N1pdm09 of the three individual vaccine arms versus placebo and of the seasonal vaccine versus its matched placebo could not be estimated due to the lack of events in the corresponding reference arm (Table 3). When comparing study subjects allocated to H1N1pdm09 vaccine rather than the matched placebo, regardless of whether they subsequently received seasonal vaccine or placebo, the vaccine efficacy against confirmed H1N1pdm09 was 65% (95% CI: -281, 97). When comparing study subjects allocated to seasonal vaccine rather than the matched placebo, regardless of whether they had previously received H1N1pdm09 vaccine or placebo, the vaccine efficacy against seasonal influenza A(H3N2) was 31% (95% CI: -138, 80) and against influenza B was 96% (95% CI: 67, 99).

DISCUSSION

In our study the efficacy of H1N1pdm09 LAIV against confirmed H1N1pdm09 infection was estimated as 65% (95% CI: -281, 97), which is consistent with case-control studies that have reported effectiveness point estimates of 61% for monovalent live attenuated H1N1pdm09 vaccine [4] and 72%-97% against confirmed influenza for other H1N1pdm09 vaccines [5-13]. Compared to two doses of placebo,

the combination of H1N1pdm09 plus seasonal influenza vaccine was estimated to have high efficacy against influenza B (VE=97%, 95% CI: 49, 100). Prior receipt of the monovalent H1N1pdm09 vaccine did not appear to reduce the efficacy of the seasonal vaccine against influenza B.

Efficacy against seasonal A(H3N2) was less clear with a wide confidence interval (VE=29%, 95% CI: -213, 84), similar to the estimates of vaccine efficacy for seasonal influenza vaccine regardless of receipt of H1N1pdm09 vaccine or placebo (Table 3). While the confidence intervals for the seasonal vaccine efficacy estimates against A(H3N2) are wide enough to encompass substantial vaccine efficacies, one plausible explanation for a potentially lower efficacy against A(H3N2) is the significant antigenic drift between the vaccine strain and the drifted A/Perth/16/09 (H3N2)-like viruses that circulated during the summer of 2010 in Hong Kong. It is possible that vaccine efficacy could have declined during the 6-month period between administration of the seasonal vaccine and local A(H3N2) activity, although the literature suggests that LAIV protection could last for a year or more [23,24]. The estimates of the efficacy of the seasonal LAIV against seasonal influenza, ARI and FARI are similar to estimates of the efficacy of seasonal trivalent inactivated influenza vaccination in school-age children in Hong Kong from a separate study conducted in the same year [17].

The major limitation of our study is that it was underpowered to identify vaccine efficacy with statistical significance, due to the moderate sample size and lower than expected attack rates of confirmed influenza. Incidence of H1N1pdm09 was low in children in 2010, following the first pandemic wave (June-October 2009) during

which around half of school-age children were estimated to have had H1N1pdm09 infection [25]. Furthermore, our estimates of vaccine efficacy may be conservative given that some participating children may have been immune prior to vaccination. The prevalent seasonal A(H3N2) viruses in the summer of 2010 were antigenically similar to the A/Perth/16/09 (H3N2)-like virus that had circulated in Hong Kong in the summer of 2009 [15] and to which many children had been exposed during that period [16]. With only a small number of children aged 7-8 who had not previously been vaccinated, we could not explore whether vaccine efficacy was lower in these children. Other limitations of this report include the lack of a serologic endpoint, since it is unlikely that we were able to confirm all influenza infections by RT-PCR despite intensive prospective follow-up [16,17]. Finally, study subjects who received vaccine may have experienced milder illness and reduced viral shedding if infected with influenza, reducing the probability of confirming infection with laboratory testing. Herd immunity [26-28] is unlikely to have affected our results given the low participation rate in individual classes. Among children who did not participate in our study, uptake of the 2009 H1N1pdm09 vaccine and the 2009-10 seasonal influenza vaccine was very low [17,29].

Higher rates of adverse events reported for the H1N1pdm09 vaccine than the seasonal vaccine (Appendix Figure 2) are unlikely to reflect greater reactogenicity of the H1N1pdm09 vaccine because of the similarly high rates for the matching placebo. One possible explanation is that the earlier timing of H1N1pdm09/placebo administration coincided with colder weather or a period of co-circulation of other respiratory pathogens, although the latter is less likely if the H1N1pdm09 vaccine were to provide short-term immunity against other respiratory infections [30].

Another explanation is greater awareness of symptoms during that period, or greater anxiety about receipt of a new vaccine.

In conclusion, our results are consistent with the anticipated benefits associated with receipt of H1N1pdm09 and seasonal influenza vaccine. Our study demonstrated efficacy of seasonal vaccination against well-matched influenza B even when preceded by monovalent H1N1pdm09 vaccination, and limited adverse effects of vaccination. Following the pandemic, the seasonal A(H1N1) strain has been replaced in influenza vaccines by a H1N1pdm09 strain so that only one vaccine is required to protect against all strains predicted to circulate. In preparation for future pandemics, maximum benefit would be gained from timely availability of an effective vaccine.

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Table 1. Baseline characteristics of study subjects by study arm.

Characteristic	Seasonal & H1N1 (n=272) n (%)	H1N1 (n=143) n (%)	Seasonal (n=143) n (%)	Placebo (n=145) n (%)	p-value*
Female	144 (53)	76 (53)	73 (51)	76 (52)	0.98
Age group					
7-8 years	99 (36)	44 (30)	41 (29)	45 (31)	0.37
9-11 years	173 (64)	99 (70)	102 (71)	100 (69)	
Received influenza vaccination prior to the 2008-09 season (%)	61 (22)	32 (22)	38 (27)	31 (21)	0.72
Mean number of household members (sd)	4.3 (1.1)	4.1 (1.1)	4.1 (1.0)	4.2 (1.0)	0.24
Educational attainment of household head					
College	63 (23)	35 (24)	31 (22)	36 (25)	0.85
Secondary or Primary	187 (69)	96 (67)	105 (73)	100 (69)	
Unknown	22 (8)	12 (8)	7 (5)	9 (6)	

* p-values estimated by chi-squared tests.

Table 2. Incidence rates of confirmed influenza infections and acute respiratory illnesses among study subjects who received 2009 monovalent pandemic H1N1 (H1N1pdm09) vaccine and/or seasonal trivalent vaccine, or placebo. Incidence rates are estimated per 1,000 person-months of follow-up, with 95% confidence intervals.

Outcomes	H1N1pdm09 &				p-value
	seasonal	H1N1pdm09	Seasonal	Placebo	
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	
	(n=272)	(n=143)	(n=143)	(n=145)	
RT-PCR confirmed influenza:					
Pandemic A(H1N1 pdm09)	0.4 (0.0, 1.3)	0.0 (0.0, 0.6)	1.6 (0.0, 3.9)	0.0 (0.0, 0.6)	0.27
Seasonal A(H3N2)	1.7 (0.0, 3.4)	1.6 (0.0, 3.9)	0.8 (0.0, 2.4)	2.4 (0.0, 5.2)	0.83
Seasonal B	0.0 (0.0, 0.3)	5.8 (1.5, 10.0)	0.8 (0.0, 2.4)	7.3 (2.5, 12.1)	<0.01
FARI	57.1 (48.1, 67.7)	62.5 (49.9, 78.3)	68.3 (55.1, 84.7)	74.6 (60.8, 91.6)	0.23

	147.5 (132.6,	140.7 (121.1,	163.7 (142.5,	189.9 (167.0,	0.01
ARI	164.0)	163.4)	188.1)	215.8)	

* p-values calculated by Fisher's exact tests for RT-PCR confirmed infections and Wald tests under Poisson regression for ARI and ILI.

† FARI defined as fever $\geq 37.8^{\circ}\text{C}$ plus cough or sore throat; ARI defined as at least two of fever $\geq 37.8^{\circ}\text{C}$, sore throat, cough, headache, myalgia.

Table 3. Vaccine efficacies against confirmed influenza, influenza-like illness and acute respiratory illness, with 95% confidence intervals.

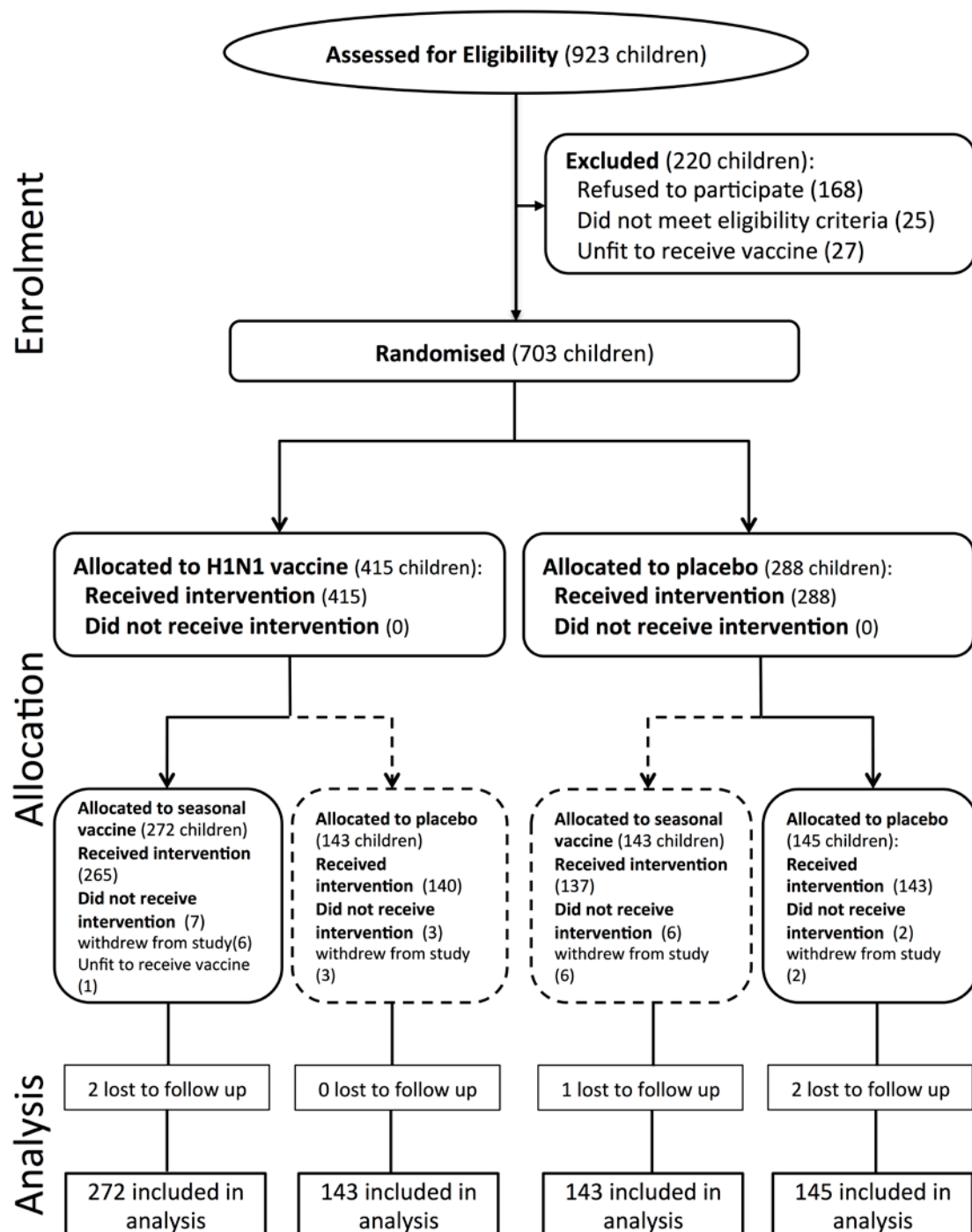
Live attenuated vaccines	Against RT-PCR-confirmed influenza			Against febrile acute	Against acute
	H1N1pdm09	A(H3N2)	B	respiratory illness [†]	respiratory illness [†]
Compared to placebo/placebo:					
(I vs IV): H1N1pdm09 plus seasonal	n/a [‡]	0.29 (-2.13, 0.84)	0.97 (0.49, 1.00)	0.24 (0.00, 0.41)	0.22 (0.08, 0.34)
(II vs IV): H1N1pdm09	n/a [‡]	0.32 (-2.99, 0.89)	0.21 (-1.06, 0.70)	0.16 (-0.14, 0.38)	0.26 (0.10, 0.39)
(III vs IV): seasonal	n/a [‡]	0.66 (-2.21, 0.96)	0.89 (0.12, 0.99)	0.09 (-0.23, 0.32)	0.14 (-0.04, 0.29)
Compared to matched placebo regardless of the other vaccine:					
(I/II vs III/IV): H1N1pdm09	0.65 (-2.81, 0.97)	-0.04 (-2.66, 0.70)	0.51 (-0.26, 0.81)	0.18 (-0.01, 0.33)	0.18 (0.07, 0.28)
(I/III vs II/IV): seasonal	n/a [‡]	0.31 (-1.38, 0.80)	0.96 (0.67, 0.99)	0.11 (-0.09, 0.27)	0.07 (-0.05, 0.19)

* Influenza vaccine efficacies derived by comparing incidence rates in study arms: I= H1N1pdm09 vaccine plus seasonal trivalent vaccine; II=H1N1pdm09 vaccine plus placebo; III=seasonal trivalent vaccine plus placebo; IV=two doses of placebo. VE = (1-relative risk)×100.

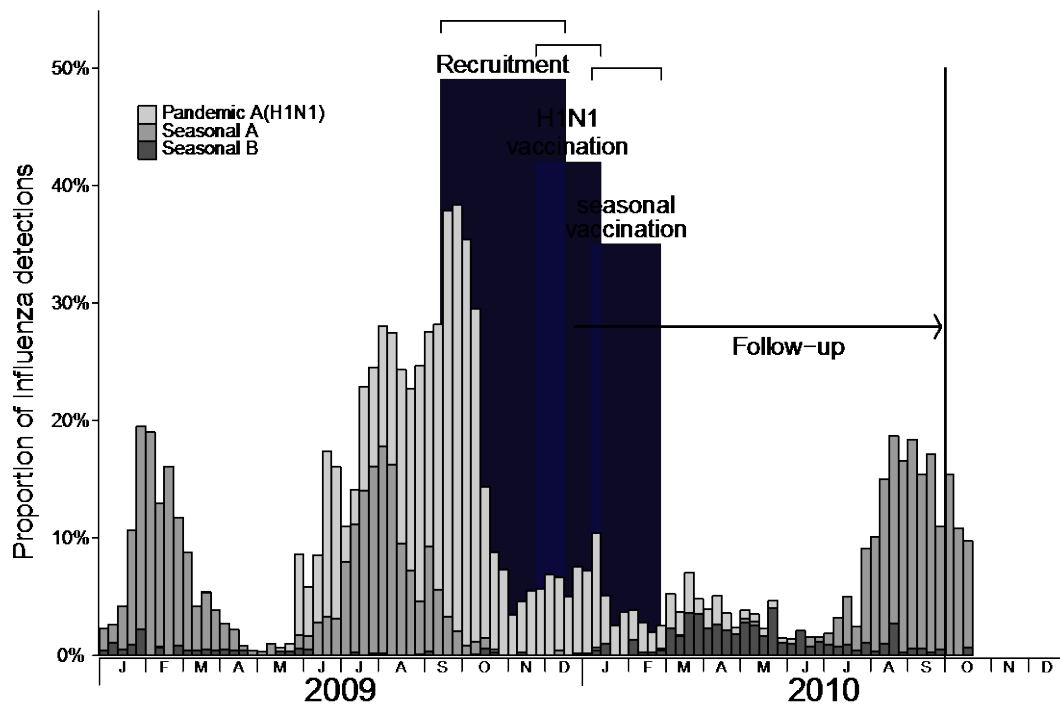
[†] FARI defined as fever $\geq 37.8^{\circ}\text{C}$ plus cough or sore throat; ARI defined as at least two of fever $\geq 37.8^{\circ}\text{C}$, sore throat, cough, headache, myalgia.

[‡] could not be estimated due to an insufficient number of events.

Figure 1. Flow of subjects through the study



Appendix Figure 1. Study timeline in relation to influenza detections reported by the World Health Organization reference laboratory at Queen Mary Hospital, Hong Kong.



Appendix Figure 2. Adverse events classified as mild or moderate reported by recipients of H1N1pdm09 vaccination or placebo (left) and seasonal vaccination or placebo (right). Statistically significant differences at $p < 0.05$ are highlighted with an asterisk.

